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(54) **O-ALKYLATED RAPAMYCIN DERIVATIVE AND ITS USE, PARTICULARLY AS IMMUNOSUPPRESSANT**

O-ALKYLIERTE RAPAMYCIN-DERIVAT UND SEINE VERWENDUNG INSBESONDERE ALS IMMUNOSUPPRESSIVA

DERIVE O-ALKYLE DE LA RAPAMYCINE ET SON UTILISATION, EN PARTICULIER COMME IMMUNOSUPPRESSEUR

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(56) References cited:
US-A- 5 120 842 **US-A- 5 151 413**

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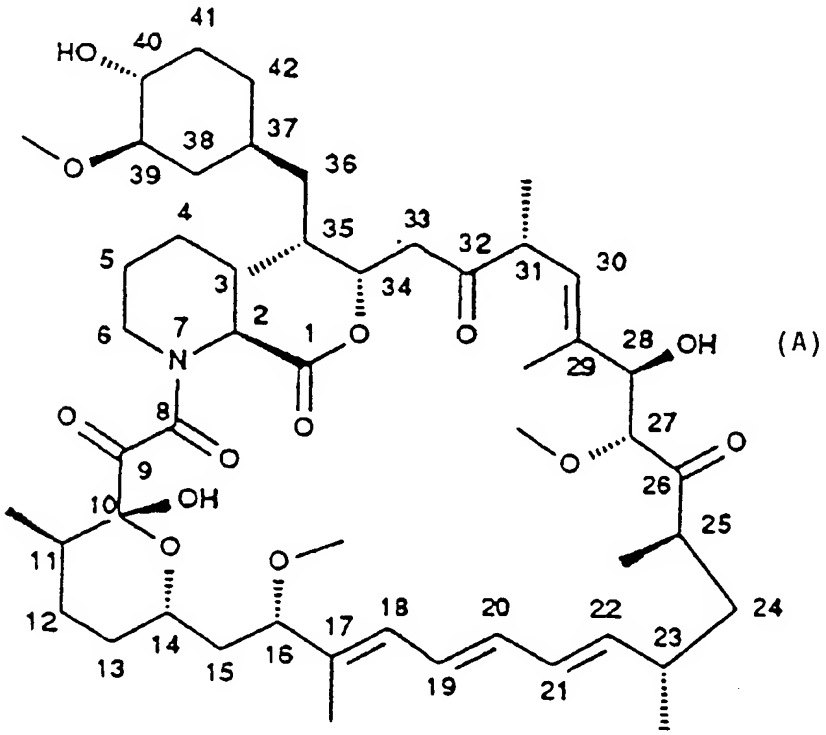
Description

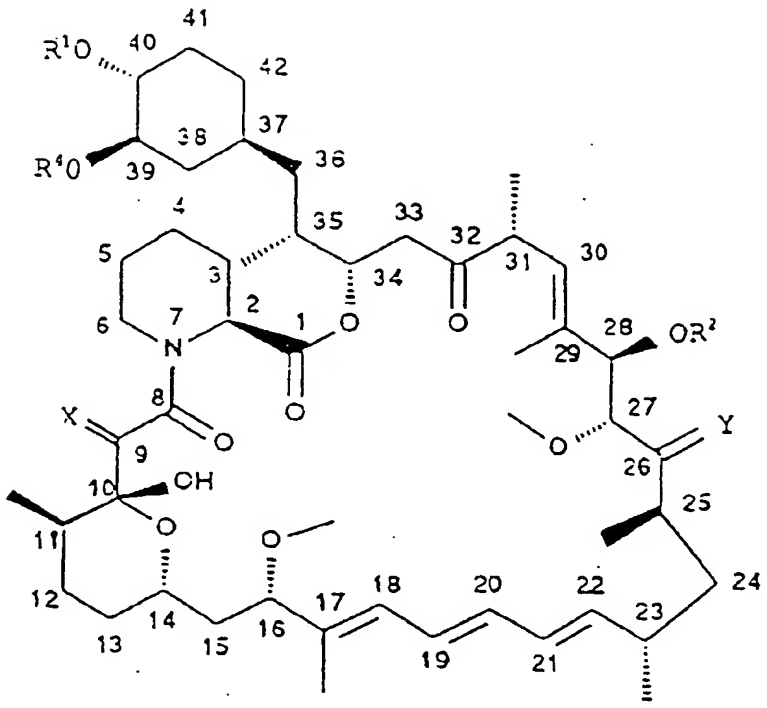
This invention comprises a novel alkylated derivative of rapamycin having pharmaceutical utility, especially as immunosuppressant.

Rapamycin is a known macrolide antibiotic produced by Streptomyces hygroscopicus, having the structure depicted in Formula A:



See, e.g.. McAlpine J.B., et al., J. Antibiotics (1991) 44: 688; Schreiber, S.L., et al., J. Am. Chem. Soc. (1991) 113: 7433; US Patent No. 3 929 992. Rapamycin is an extremely potent immunosuppressant and has also been shown to have antitumor and antifungal activity. Its utility as a pharmaceutical, however, is restricted by its very low and variable bioavailability as well as its high toxicity. Moreover, rapamycin is highly insoluble, making it difficult to formulate stable galenic compositions.

It has now surprisingly been discovered that a novel derivative of rapamycin (the Novel Compound) has an improved pharmacologic profile over rapamycin, exhibits greater stability and bioavailability, and allows for greater ease in producing galenic formulations. The Novel Compound is an alkylated derivative of rapamycin having the structure of Formula I:



(I)

wherein

R_1 is $-CH_2CH_2-OH$,
R_2 is H,
R_4 is methyl,
X is O, and
Y is O.

Preferably, O-substitution at C40 is performed according to the following general process: Rapamycin is reacted with an organic radical attached to a leaving group (e.g., RX where R is the organic radical, e.g., an alkyl which is desired as the O-substituent, and X is the leaving group, e.g., $CCl_3C(NH)O$ or CF_3SO_3) under suitable reaction conditions, preferably acidic or neutral conditions, e.g., in the presence of an acid like trifluoromethanesulfonic acid, camphorsulfonic acid, p-toluenesulfonic acid or their respective pyridinium or substituted pyridinium salts when X is $CCl_3C(NH)O$ or in the presence of a base like pyridine, a substituted pyridine, diisopropylethylamine or pentamethylpiperidine when X is CF_3SO_3.

The Novel Compound is particularly useful for the following conditions:

a) Treatment and prevention of organ or tissue transplant rejection, e.g. for the treatment of recipients of e.g. heart, lung, combined heart-lung, liver, kidney, pancreatic, skin or corneal transplants. It is also indicated for the prevention of graft-versus-host disease, such as following bone marrow transplantation.

b) Treatment and prevention of autoimmune disease and of inflammatory conditions, in particular inflammatory conditions with an etiology including an autoimmune component such as arthritis (for example rheumatoid arthritis, arthritis chronica progred iente and arthritis deformans) and rheumatic diseases. Specific autoimmune diseases for which the compound of the invention may be employed include, autoimmune hematological disorders (including e.g. hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis and Crohn's disease) endocrine ophthalmopathy, Graves disease, sarcoido-

sis, multiple sclerosis, primary billiary cirrhosis, juvenile diabetes (diabetes mellitus type I), uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis, glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy) and juvenile dermatomyositis.

c) Treatment and prevention of asthma.

d) Treatment of multi-drug resistance (MDR). The Novel Compound suppresses P-glycoproteins (Pgp), which are the membrane transport molecules associated with MDR. MDR is particularly problematic in cancer patients and AIDS patients who will not respond to conventional chemotherapy because the medication is pumped out of the cells by Pgp. The Novel Compound is therefore useful for enhancing the efficacy of other chemotherapeutic agents in the treatment and control of multidrug resistant conditions such as multidrug resistant cancer or multidrug resistant AIDS.

e) Treatment of proliferative disorders, e.g. tumors, hyperproliferative skin disorder and the like.

f) Treatment of fungal infections.

g) Treatment and prevention of inflammation, especially in potentiating the action of steroids.

h) Treatment and prevention of infection, especially infection by pathogens having Mip or Mip-like factors.

The invention thus provides the Novel Compound described herein, for use as novel intermediate or as pharmaceutical, methods of treating or preventing the above-described disorders by administering an effective amount of the Novel Compound to a patient in need thereof, use of the Novel Compound in the manufacture of a medicament for treatment or prevention of the above-described disorders, and pharmaceutical compositions comprising the Novel Compound in combination or association with a pharmaceutically acceptable diluent or carrier.

The Novel Compound described herein is highly immunosuppressive, and is particularly useful in indications a and b.

The Novel Compound is utilized by administration of a pharmaceutically effective dose in pharmaceutically acceptable form to a subject in need of treatment. Appropriate dosages of the Novel Compound will of course vary, e.g. depending on the condition to be treated (for example the disease type or the nature of resistance), the effect desired and the mode of administration.

In general however satisfactory results are obtained on administration orally at dosages on the order of from 0.05 to 5 or up to 10mg/kg/day, e.g. on the order of from 0.1 to 2 or up to 7.5 mg/kg/day administered once or, in divided doses 2 to 4x per day, or on administration parenterally, e.g. intravenously, for example by i.v. drip or infusion, at dosages on the order of from 0.01 to 2.5 up to 5 mg/kg/day, e.g. on the order of from 0.05 or 0.1 up to 1.0 mg/kg/day. Suitable daily dosages for patients are thus on the order of 500 mg p.o., e.g. on the order of from 5 to 100 mg p.o., or on the order of from 0.5 to 125 up to 250 mg i.v., e.g. on the order of from 2.5 to 50 mg i.v..

Alternatively and even preferably, dosaging is arranged in patient specific manner to provide pre-determined trough blood levels, e.g. as determined by RIA technique. Thus patient dosaging may be adjusted so as to achieve regular on-going trough blood levels as measured by RIA on the order of from 50 or 150 up to 500 or 1000ng/ml, i.e. analogously to methods of dosaging currently employed for Ciclosporin immunosuppressive therapy.

The Novel Compound may be administered as the sole active ingredient or together with other drugs. For example, in immunosuppressive applications such as prevention and treatment of graft vs. host disease, transplant rejection, or autoimmune disease, the Novel Compound may be used in combination with Ciclosporin, FK-506, or their immunosuppressive derivatives; corticosteroids; azathioprene; immunosuppressive monoclonal antibodies, e.g., monoclonal antibodies to CD3, CD4, CD25, CD28, or CD45; and /or other immunomodulatory compounds. For anti-inflammatory applications, the Novel Compound can be used together with anti-inflammatory agents, e.g., corticosteroids. For anti-infective applications, the Novel Compound can be used in combination with other anti-infective agents, e.g., anti-viral drugs or antibiotics.

The Novel Compound is administered by any conventional route, in particular enterally, e.g. orally, for example in the form of solutions for drinking, tablets or capsules or parenterally, for example in the form of injectable solutions or suspensions. Suitable unit dosage forms for oral administration comprise, e.g. from 1 to 50 mg of a compound of the invention, usually 1 to 10 mg. Pharmaceutical compositions comprising the novel compound may be prepared analogously to pharmaceutical compositions comprising rapamycin, e.g., as described in EPA 0 041 795, which would be evident to one skilled in the art.

The pharmacological activity of the Novel Compound is demonstrated in, e.g., the following tests:

1. Mixed lymphocyte reaction (MLR)

The Mixed Lymphocyte Reaction was originally developed in connection with allografts, to assess the tissue compatibility between potential organ donors and recipients, and is one of the best established models of immune reaction in vitro. A murine model MLR, e.g., as described by T.Meo in "Immunological Methods", L. Lefkovits and B. Peris, Eds.,

Academic Press, N.Y. pp. 227-239 (1979), is used to demonstrate the immunosuppressive effect of the Novel Compound. Spleen cells (0.5×10^6) from Balb/c mice (female, 8-10 weeks) are co-incubated for 5 days with 0.5×10^6 irradiated (2000 rads) or mitomycin C treated spleen cells from CBA mice (female, 8-10 weeks). The irradiated allogeneic cells induce a proliferative response in the Balb/c spleen cells which can be measured by labeled precursor incorporation into the DNA. Since the stimulator cells are irradiated (or mitomycin C treated) they do not respond to the Balb/c cells with proliferation but do retain their antigenicity. The antiproliferative effect of the Novel Compound on the Balb/c cells is measured at various dilutions and the concentration resulting in 50% inhibition of cell proliferation (IC_{50}) is calculated. The inhibitory capacity of the test sample may be compared to rapamycin and expressed as a relative IC_{50} (i.e. IC_{50} test sample/IC_{50} rapamycin).

2. IL-6 mediated proliferation

The capacity of the Novel Compound to interfere with growth factor associated signalling pathways is assessed using an interleukin-6 (IL-6)-dependent mouse hybridoma cell line. The assay is performed in 96-well microtiter plates. 5000 cells/well are cultivated in serum-free medium (as described by M. H. Schreier and R. Tees in Immunological Methods, I. Lefkovits and B. Pernis, eds., Academic Press 1981, Vol. II, pp. 263-275), supplemented with 1 ng recombinant IL-6/ml. Following a 66 hour incubation in the absence or presence of a test sample, cells are pulsed with 1 µCi (3-H)-thymidine/well for another 6 hours, harvested and counted by liquid scintillation. (3-H)-thymidine incorporation into DNA correlates with the increase in cell number and is thus a measure of cell proliferation. A dilution series of the test sample allows the calculation of the concentration resulting in 50% inhibition of cell proliferation (IC_{50}). The inhibitory capacity of the test sample may be compared to rapamycin and expressed as a relative IC_{50} (i.e. IC_{50} test sample/ IC_{50} rapamycin).

3. Macrophilin binding assay

Rapamycin and the structurally related immunosuppressant, FK-506, are both known to bind in vivo to macrophilin-12 (also known as FK-506 binding protein or FKBP-12), and this binding is thought to be related to the immunosuppressive activity of these compounds. The Novel Compound also binds strongly to macrophilin-12, as is demonstrated in a competitive binding assay.

In this assay, FK-506 coupled to BSA is used to coat microtiter wells. Biotinylated recombinant human macrophilin-12 (biot-MAP) is allowed to bind in the presence or absence of a test sample to the immobilized FK-506. After washing (to remove non-specifically bound macrophilin), bound biot-MAP is assessed by incubation with a streptavidin-alkaline phosphatase conjugate, followed by washing and subsequent addition of p-nitrophenyl phosphate as a substrate. The read-out is the OD at 405nm. Binding of a test sample to biot-MAP results in a decrease in the amount of biot-MAP bound to the FK-506 and thus in a decrease in the OD405. A dilution series of the test sample allows determination of the concentration resulting in 50% inhibition of the biot-MAP binding to the immobilized FK-506 (IC_{50}). The inhibitory capacity of a test sample is compared to the IC_{50} of free FK-506 as a standard and expressed as a relative IC_{50} (i.e., IC_{50}-test sample/ IC_{50}-free FK-506).

4. Localized Graft-Versus-Host (GvH) Reaction

In vivo efficacy of the Novel Compound is proved in a suitable animal model, as described, e.g., in Ford et al, TRANSPLANTATION 10 (1970) 258. Spleen cells (1×10^7) from 6 week old female Wistar/Furth (WF) rats are injected subcutaneously on day 0 into the left hind-paw of female (F344 x WF)F_1 rats weighing about 100g. Animals are treated for 4 consecutive days and the popliteal lymph nodes are removed and weighed on day 7. The difference in weight between the two lymph nodes is taken as the parameter for evaluating the reaction.

5. Kidney Allograft Reaction in Rat

One kidney from a female fisher 344 rat is transplanted onto the renal vessel of a unilaterally (left side) nephrectomized WF recipient rat using an end-to-end anastomosis. Ureteric anastomosis is also end-to-end. Treatment commences on the day of transplantation and is continued for 14 days. A contralateral nephrectomy is done seven days after transplantation, leaving the recipient relying on the performance of the donor kidney. Survival of the graft recipient is taken as the parameter for a functional graft.

6. Experimentally Induced Allergic Encephalomyelitis (EAE) in Rats

Efficacy of the Novel Compound in EAE is measured, e.g., by the procedure described in Levine & Wenk, AMER

J PATH 47 (1965) 61; McFarlin et al, J IMMUNOL 113 (1974) 712; Borel, TRANSPLANT. & CLIN. IMMUNOL 13 (1981) 3. EAE is a widely accepted model for multiple sclerosis. Male Wistar rats are injected in the hind paws with a mixture of bovine spinal cord and complete Freund's adjuvant. Symptoms of the disease (paralysis of the tail and both hind legs) usually develop within 16 days. The number of diseased animals as well as the time of onset of the disease are recorded.

7. Freund's Adjuvant Arthritis

Efficacy against experimentally induced arthritis is shown using the procedure described, e.g., in Winter & Nuss, ARTHRITIS & RHEUMATISM 9 (1966) 394; Billingham & Davies, HANDBOOK OF EXPERIMENTAL PHARMACOL (Vane & Ferreira Eds, Springer-Verlag, Berlin) 50/II (1979) 108-144. OFA and Wistar rats (male or female, 150g body weight) are injected i.c. at the base of the tail or in the hind paw with 0.1 ml of mineral oil containing 0.6 mg of lyophilized heat-killed Mycobacterium smegmatis. In the developing arthritis model, treatment is started immediately after the injection of the adjuvant (days 1 - 18); in the established arthritis model treatment is started on day 14, when the secondary inflammation is well developed (days 14-20). At the end of the experiment, the swelling of the joints is measured by means of a micro-caliper. ED_{50} is the oral dose in mg/kg which reduces the swelling (primary or secondary) to half of that of the controls.

8. Antitumor and MDR activity

The antitumor activity of the Novel Compound and its ability to enhance the performance of antitumor agents by alleviating multidrug resistance is demonstrated, e.g., by administration of an anticancer agent, e.g., colchicine or etoposide, to multidrug resistant cells and drug sensitive cells in vitro or to animals having multidrug resistant or drug sensitive tumors or infections, with and without co-administration of the Novel Compound to be tested, and by administration of the Novel Compound alone.

Such in vitro testing is performed employing any appropriate drug resistant cell line and control (parental) cell line, generated, e.g. as described by Ling et al., J. Cell. Physiol. 83, 103-116 (1974) and Bech-Hansen et al. J. Cell. Physiol. 88, 23-32 (1976). Particular clones chosen are the multi-drug resistant (e.g. colchicine resistant) line CHR (subclone C5S3.2) and the parental, sensitive line AUX BI (subclone ABI S11).

In vivo anti-tumor and anti-MDR activity is shown, e.g., in mice injected with multidrug resistant and drug sensitive cancer cells. Ehrlich ascites carcinoma (EA) sub-lines resistant to drug substance DR, VC, AM, ET, TE or CC are developed by sequential transfer of EA cells to subsequent generations of BALB/c host mice in accordance with the methods described by Slater et al., J. Clin. Invest, 70, 1131 (1982).

Equivalent results may be obtained employing the Novel Compound test models of comparable design, e.g. in vitro, or employing test animals infected with drug -resistant and drug sensitive viral strains, antibiotic (e.g. penicillin) resistant and sensitive bacterial strains, anti-mycotic resistant and sensitive fungal strains as well as drug resistant protozoal strains, e.g. Plasmodial strains, for example naturally occurring sub-strains of Plasmodium falciparum exhibiting acquired chemotherapeutic, anti-malarial drug resistance.

9. Steroid potentiation

The macrophilin binding activity of the Novel Compound also makes them useful in enhancing or potentiating the action of corticosteroids. Combined treatment with the compounds of the invention and a corticosteroid, such as dexamethasone, results in greatly enhanced steroidal activity. This can be shown, e.g., in the murine mammary tumor virus-chloramphenicol acetyltransferase (MMTV-CAT) reporter gene assay, e.g., as described in Ning, et al., *J. Biol. Chem.* (1993) **268**: 6073. This synergistic effect allows reduced doses of corticosteroids, thereby reducing the risk of side effects in some cases.

10. Mip and Mip-like factor inhibition

Additionally, the Novel Compound binds to and blocks a variety of Mip (macrophage infectivity potentiator) and Mip-like factors, which are structurally similar to macrophilin. Mip and Mip-like factors are virulence factors produced by a wide variety of pathogens, including those of the genera Chlamidia, e.g., Chlamidia trachomatis; Neisseria, e.g., Neisseria meningitidis; and Legionella, e.g., Legionella pneumophilia; and also by the obligately parasitic members of the order Rickettsiales. These factors play a critical role in the establishment of intracellular infection. The efficacy of the Novel Compound in reducing the infectivity of pathogens which produce Mip or Mip-like factors can be shown by comparing infectivity of the pathogens in cells culture in the presence and absence of the macrolides, e.g., using the methods described in Lundemose, et al., *Mol. Microbiol.* (1993) 7: 777.

The Novel Compound is also useful in assays to detect the presence or amount of macrophilin-binding compounds, e.g., in competitive assays for diagnostic or screening purposes. Thus, in another embodiment, the invention provides for use of the Novel Compound as a screening tool to determine the presence of macrophilin-binding compounds in a test solution, e.g., blood, blood serum, or test broth to be screened. Preferably, a Novel Compound is immobilized in microtiter wells and then allowed to bind in the presence and absence of a test solution to labelled macrophilin-12 (FKBP-12). Alternatively, the FKBP-12 immobilized in microtiter wells and allowed to bind in the presence and absence of a test solution to a Novel Compound which has been labelled, e.g., fluoro-, enzymatically- or radiolabelled, e.g., a Novel Compound which has been O-substituted at C40 with a labelling group. The plates are washed and the amount of bound labelled compound is measured. The amount of macrophilin-binding substance in the test solution is roughly inversely proportional to the amount of bound labelled compound. For quantitative analysis, a standard binding curve is made using known concentrations of macrophilin bind compound.

EXAMPLES:

In the following examples, characteristic spectroscopic data is given to facilitate identification. Peaks which do not differ significantly from rapamycin are not included. Biological data is expressed as a relative IC_{50}, compared to rapamycin in the case of the mixed lymphocyte reaction (MLR) and IL-6 dependent proliferation (IL-6 dep. prol.) assays, and to FK-506 in the macrophilin binding assay (MBA). A higher IC_{50} correlates with lower binding affinity.

Example 1: 40-O-(2-Hydroxy)ethyl-rapamycin

a) 40-O-[2-(t-Butyldimethylsilyl)oxy]ethyl-rapamycin

A solution of 9.14 g (10 mmol) of rapamycin and 4.70 mL (40 mmol) of 2,6-lutidine in 30 mL of toluene is warmed to 60°C and a solution of 6.17 g (20 mmol) of 2-(t-butyldimethylsilyl)oxyethyl triflate and 2.35 mL (20 mmol) of 2,6-lutidine in 20 mL of toluene is added. This mixture is stirred for 1.5h. Then two batches of a solution of 3.08 g (10 mmol) of triflate and 1.2 mL (10 mmol) of 2,6-lutidine in 10 mL of toluene are added in a 1.5h interval. After addition of the last batch, stirring is continued at 60°C for 2h and the resulting brown suspension is filtered. The filtrate is diluted with ethyl acetate and washed with aq. sodium bicarbonate and brine. The organic solution is dried over anhydrous sodium sulfate, filtered and concentrated. The residue is purified by column chromatography on silica gel (40:60 hexane-ethyl acetate) to afford 40-O-[2-(t-butyldimethylsilyl)oxy]ethyl-rapamycin as a white solid: ^{1}H NMR ($CDCl_3$) δ 0.06 (6H, s), 0.72 (1H, dd), 0.90 (9H, s), 1.65 (3H, s), 1.75 (3H, s), 3.02 (1H, m), 3.63 (3H, m), 3.72 (3H, m); MS (FAB) m/z 1094 ($[M+Na]^+$), 1022 ($[M-(OCH_3+H_2O)]^+$).

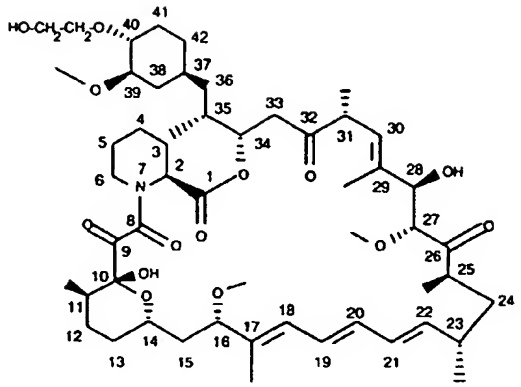
b) 40-O-(2-Hydroxy)ethyl-rapamycin

To a stirred, cooled (0°C) solution of 4.5 g (4.2 mmol) of 40-O-[2-(t-butyldimethylsilyl)oxy]ethyl-rapamycin in 20 mL of methanol is added 2 mL of 1N HCl. This solution is stirred for 2h and neutralized with aq. sodium bicarbonate. The mixture is extracted with three portions of ethyl acetate. The organic solution is washed with aq. sodium bicarbonate and brine, dried over anhydrous sodium sulfate, filtered and concentrated. Purification by column chromatography on silica gel (ethyl acetate) gave the title compound as a white solid: ^{1}H NMR ($CDCl_3$) δ 0.72 (1H, dd), 1.65 (3H, s), 1.75 (3H, s), 3.13 (5H, s and m), 3.52-3.91 (8H, m); MS (FAB) m/z 980 ($[M+Na]^+$), 926 ($[M-OCH_3]^+$), 908 ($[M-(OCH_3+H_2O)]^+$), 890 ($[M-(OCH_3+2H_2O)]^+$), 876 ($[M-(2CH_3OH+OH)]^+$), 858 ($[M-(OCH_3+CH_3OH+2H_2O)]^+$).

MBA (rel. IC50)	2.2
IL-6 dep. prol. (rel. IC50)	2.8
MLR (rel. IC50)	3.4

Claims

1. 40-O-(2-hydroxy)ethyl-rapamycin of formula



(I)

2. 40-O-(2-hydroxy)ethyl-rapamycin for use as a pharmaceutical.

3. A pharmaceutical composition comprising 40-O-(2-hydroxy)ethyl-rapamycin together with a pharmaceutically acceptable diluent or carrier.

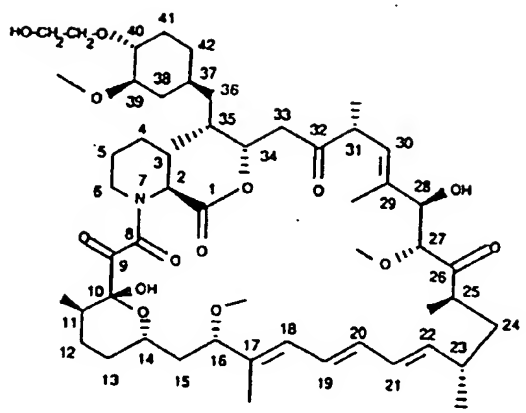
4. Use of 40-O-(2-hydroxy)ethyl-rapamycin in the manufacture of a medicament for treating or preventing allograft rejection.

5. Use of 40-O-(2-hydroxy)ethyl-rapamycin in the manufacture of a medicament for treating or preventing any of the following conditions:

   (i) autoimmune disease,
   (ii) graft vs. host disease,
   (iii) asthma,
   (iv) multidrug resistance,
   (v) tumors or hyperproliferative disorders, or
   (vi) fungal infections,
   (vii) inflammation,
   (viii) infection by pathogens having Mip or Mip-like factors, or
   (ix) overdose of macrophilin-binding immunosuppressants.

Patentansprüche

1. 40-O(2-Hydroxy)ethylrapamycin der Formel



(I)

2. 40-O(2-Hydroxy)ethylrapamycin zur Verwendung als Pharmazeutikum.

3. Pharmazeutische Zusammensetzung, die 40-O(2-Hydroxy)ethylrapamycin zusammen mit einem pharmazeutisch annehmbaren Verdünnungmittel oder Träger enthält.

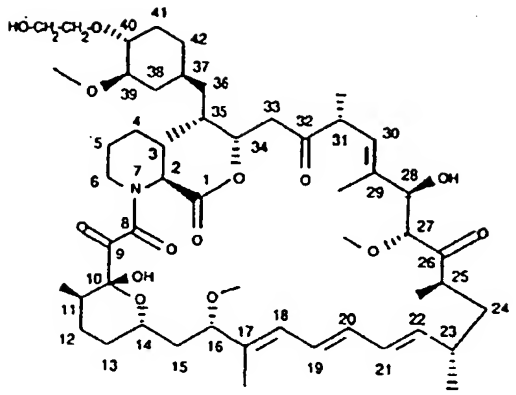
4. Verwendung von 40-O(2-Hydroxy)ethylrapamycin zur Herstellung eines Arzneimittels zur Behandlung oder Verhinderung der Allotransplantatabstoßung.

5. Verwendung von 40-O(2-Hydroxy)ethylrapamycin zur Herstellung eines Arzneimittels zur Behandlung oder Verhinderung eines der folgenden Zustände:

   (i) Autoimmunerkrankung
   (ii) Graft vs. Host Erkrankung
   (iii) Asthma
   (iv) Multiarzneimittelresistenz
   (v) Tumoren oder hyperproliferative Störungen, oder
   (vi) Pilzinfektionen
   (vii) Entzündung
   (viii) Infektion durch Pathogene mit Mip oder Mip-ähnlichen Faktoren, oder
   (ix) Überdosierung von Makrophilin-bindenden Immunsuppressiva.

Revendications

1. La 40-O-(2-hydroxy)éthyl-rapamycine de formule



(I)

2. La 40-O-(2-hydroxy)éthyl-rapamycine pour une utilisation comme médicament.

3. Une composition pharmaceutique comprenant la 40-O-(2-hydroxy)-éthyl-rapamycine ensemble avec un diluant ou véhicule pharmaceutiquement acceptable.

4. L'utilisation de la 40-O-(2-hydroxy)éthyl-rapamycine dans la fabrication d'un médicament pour le traitement ou la prévention du rejet d'une allogreffe.

5. L'utilisation de la 40-O-(2-hydroxy)éthyl-rapamycine dans la fabrication d'un médicament pour le traitement ou la prévention de l'une quelconque des conditions suivantes:

(i) une maladie autoimmune,
(ii) une maladie greffon contre hôte,
(iii) l'asthme,
(iv) la résistance à plusieurs médicaments,
(v) les tumeurs ou les troubles hyperprolifératifs, ou bien
(vi) les infections fongiques,
(vii) l'inflammation,
(viii) l'infection par des pathogènes ayant les facteurs Mip ou du type Mip, ou bien
(ix) la surdose en immunosuppresseurs se liant à la macrophiline.